recovery could be the result of rapid reabsorption of these substances which accumulate in the fluid distending the stomach, since the non-operative release of obstruction allows the obstructed content to move rapidly on to the lower parts of the canal where absorption is rapid.

To test this point, further experiments were performed in which the obstruction was released after fourteen hours, but just prior to release, the stomach was emptied of its accumulated fluid and washed with distilled water. Distilled water was left in the stomach so that loss of water was not a factor in the result. None of these animals survived. Autopsy showed that the release had been complete and that no performation or peritonitis or other observable complication existed.

Since these animals, in which the stomach was evacuated prior to release of obstruction, succumbed to a duration of obstruction which had been shown in the earlier series of experiments to be a non-fatal duration, the experiments indicate that the cause of early death of rabbits with high intestinal obstruction is not due to dehydration, nor absorption of a toxic substance, nor extreme gastric dilatation, but to a loss in the gastric contents of something essential to the animal's recovery. This loss is likely the chloride and sodium as held by the writers referred to above.

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Influence of continued administration of morphine and of withdrawal on contraction of small intestines of dogs.

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Two experiments were carried out on dogs with Thiry-Vella fistulae of ileum. The operations for formation of the fistulae were performed several weeks before the experiments were started. Graphic records of the intestinal contractions were made by introducing into the fistula a sausage-shaped rubber balloon fastened on a catheter and filled with water; the catheter was connected with a Brodie bellows-recorder which made the tracing on

a slowly moving kymograph. Records were made in this way without anesthesia or operative procedure or discomfort to the animal.

Experiment 1. Ascending doses of morphine sulphate: A female collie dog, weighing 21 kg. received daily hypodermic injections for 71 days and during this time the dose was increased from 1 mg. per kg. to 25 mg. per kg. There was some constipation and loss of appetite but the dog remained in good condition, losing only one kg. in weight. Narcosis and vomiting disappeared after the fourth week, but salivation continued throughout the experiment. The dog became shy and restless as the experiment progressed.

Graphic records of the effect of the injections of morphine on the intestinal contractions were made at intervals of two to three days throughout the experiment. There was no change in the character of the reaction at any time. We have reported in a recent paper[1] that hypodermic injections of morphine in dogs greatly increase the muscular activity of the intestine. In this experiment each injection produced the usual reaction; marked increase in tone and in amplitude and frequency of the contractions. From time to time small doses (0.15 mg. per kg.) were injected before the regular daily dose, and these invariably produced stimulation of the intestinal contractions. The reaction following a small dose was as great at the end of the experiment, when the daily dose was 25 mg. per kg., as it had been at the beginning.

The administration of morphine was discontinued entirely on the 72nd day of the experiment. During the first 10 days of the withdrawal period there was a marked increase in the frequency and amplitude of the intestinal contractions. At this time the dog had diarrhea. The animal slept more than usual during the early part of the withdrawal and for a time was hard to control while the tracings were being made.

Experiment 2. Daily repetition of a small dose of morphine sulphate: A female collie dog, weighing 23 kg., received daily injections of 0.1 mg. per kg. for six weeks. Records of intestinal contractions were made every second or third day. This small dose continued to produce stimulation of the intestinal contractions throughout the experiment, the reaction being as marked

[1] Plant, O. H., and Miller, G. H., *J. Pharm. and Exp. Therap.*, (in press).

after 6 weeks as when the injections were started. Narcosis, nausea and vomiting disappeared after 2 weeks, and from that time to the end of the experiment the dog appeared normal in every way. The loss in weight amounted to 2.5 kg., but appetite remained good. Administration was stopped on the 42nd day. No changes could be observed in the intestinal contractions or in behavior during the withdrawal period.

These results show that tolerance is not developed to the stimulating effect of morphine on the intestinal contractions. They thus parallel the observations of van Egmond[2] that the cardiac vagus center does not become tolerant to morphine in dogs. Further, they indicate that the increased destruction of morphine in the tissues, which was demonstrated by Faust,[3] is not the only factor concerned in the development of morphine tolerance.

[2] van Egmond, A. A. J., *Arch. f. exp. Path. u. Pharmak.*, 1911, lxv, 197.
[3] Faust, E. S., *Arch. f. exp. Path. u. Pharmak.*, 1900, xliv, 217.